REMARKS

STATUS OF THE CLAIMS.

Claims 1, 3-19, and 23, and 25 are pending with entry of this amendment, claims 20, 21, and 24 being canceled without prejudice. Claim 1 is amended herein. Support for this amendment is found in Applicants' specification at least at page 15, lines 12-15 and page 16, lines 5-6. Accordingly, no new matter has been added by this amendment.

INTERVIEW SUMMARY.

Applicants thank the Examiner for the helpful telephonic interview held with the Examiner on June 30, 2004. Applicants' Attorney explained to the Examiner that the application of target solutions comprising amplification products to a substrate to produce an array of polypeptides (claim 1(d)) refers to the use of target solutions to produce target elements of an array and not to the use of target solutions to probe an array. Although Applicants believe that the claims, as previously written, would be clear to one skilled in the art, several possible amendments to claim 1 were discussed in the interest of expediting prosecution.

Applicants' Attorney emphasized that the art of record neither teaches nor suggests the use of the amplification method recited in claim 1 to produce target solutions that are immobilized on a substrate to produce an array of polynucleotides. In particular, Applicants' Attorney pointed out that the Declaration Under 37 C.F.R. § 1.132 of Dr. Donna G. Albertson (dated October 14, 2003) demonstrates that satisfactory polynucleotide arrays could be constructed using the claimed amplification method, but not another amplification method. Moreover, Dr. Albertson testified that she believed, prior to comparing these two methods, that the second method (*i.e.*, not the claimed method) would be most likely to work. Applicants' Attorney pointed out that this Declaration establishes the unpredictability in this field and unexpected results sufficient to rebut any *prima facie* case of obviousness. The Examiner agreed to revisit the Declaration in light of the amendment to claim 1.

REJECTIONS UNDER 35 U.S.C. §103(a).

BROWN AND SMITH

I. INTRODUCTION.

Claims 1, 3-16, 20, 23 and 25 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al. (USPN 5,807,522) in view of Smith (PCR Methods and Applications (1992) 2:71-72). Office Action, page 2. The rejection is moot as to claim 20. With respect to the remaining claims, this rejection is respectfully traversed.

Of the pending rejected claims, only claim 1 is independent. The method of claim 1 employs "a plurality of samples of double-stranded polynucleotide fragments, wherein each sample is derived from a first [i.e., a starting] polynucleotide." According to the method, each sample is amplified to form an amplification product that is "representative of the corresponding first polynucleotide." Target solutions containing the amplification products are then applied to one or more substrates, "whereby target solution polynucleotides are immobilized on the substrate(s) to form the target elements of an array of polynucleotides." It is important to note that the specifically recited amplification steps consistently produce amplification products that are highly representative of the starting polynucleotides. This feature of the invention facilitates quantitative comparison among hybridization signals produced when the target solutions are arrayed and hybridized with sample polynucleotides.

The three elements of a *prima facie* case of obviousness are: (1) the reference(s) must teach or suggest all of the elements of the claimed invention, (2) there must be some motivation for combining or modifying the teachings of the references to arrive at the claimed invention, and (3) the reference(s) or knowledge in the art must provide a reasonable expectation of success, *i.e.*, a reasonable assurance that the claimed invention would work. Applicants maintain that the Examiner has failed to establish any of the elements of a *prima facie* case of obviousness for the reasons discussed in the previous Response (filed October 15, 2003). However, rather than reiterate these arguments in detail, Applicants wish to focus on the last two elements required to establish obviousness.

II. THE RECORD IS DEVOID OF ANY MOTIVATION FOR MODIFYING BROWN AND SMITH TO ARRIVE AT THE INVENTION OF CLAIM 1.

A. Smith provides specific motivation for using ligation-mediated PCR products as probe polynucleotides, but not as target polynucleotides, for a polynucleotide array.

The Examiner acknowledges that "Brown does not teach preparing an array of specific PCR products, such as those from a ligation-mediated PCR reaction. Office Action, page 3. Applicants agree. The Examiner cites Smith as remedying this deficiency. According to the Examiner, "Smith teaches that his PCR products can be used in arraying high-density grids (*e.g.*, polynucleotide arrays) (pg. 26)." Office Action, page 4. Here, Applicants strenuously disagree. As pointed out in the previous Response:

> At page 26, Smith states "it is possible that pools of tagged PCR products from the ends of heterologous DNA segments cloned in YACs or cosmids could be employed for multiplex chromosome walking in clone libraries arrayed in high density grids." Chromosome walking is technique wherein sequences from the end of a clone of interest are labeled and used as probes to identify additional clones that potentially contain flanking sequences. In this way, the sequence information for, e.g., a gene of interest can be extended. Accordingly, Smith teaches using ligation-mediated PCR products to ***probe*** conventionally created DNA arrays. Smith does not teach or suggest arraying ligation-mediated PCR products, as the Examiner states.

The term "arraying" is used in the art to refer to immobilizing ***target*** polynucleotides on a substrate to form an array of ***target*** elements. As one skilled in the art understands, "target polynucleotides" are immobilized polynucleotides that have the capacity to hybridize to the complementary "probe polynucleotide." Target polynucleotides and probe polynucleotides are used for different purposes and are therefore subjected to different manipulations. In particular, target polynucleotides are generally immobilized on a substrate, whereas probe polynucleotides are not. Probe polynucleotides are generally labeled, whereas target polynucleotides are not. Accordingly, Smith's teaching that ligation-mediated PCR products can be used to probe a DNA array, does not suggest anything about immobilizing polynucleotides on a substrate to form the target elements of a polynucleotide array.

According the Examiner, motivation for modifying the teachings of Brown to produce the claimed invention can be found in Smith. The Examiner states that "Smith provides motivation for performing ligation-mediated PCR." Office Action. Page 8. In support of this statement, the Examiner cites several advantages of ligation-mediated PCR, as follows: "'specific

fragments can be isolated without any prior knowledge of the nucleotide sequence of the target' and . . . individual, unknown fragments can be amplified 'from any DNA molecule ranging from about 50 to 250kb in size'. (pg. 21)." *Id.* These statements arguably provide ***general*** motivation to attempt the use of ligation-mediated PCR to produce DNA for any application. These statements do not provide ***specific*** motivation to modify Brown to arrive at the claimed invention, and it is specific motivation that the law requires.

The Federal Circuit emphasized the necessity for finding specific motivation in *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). There, the court stated:

> "[V]irtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983)*; *see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S. P.Q. 8, 12 (Fed. Cir. 1983)* ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d 1551, 1554 (Fed. Cir. 1996).*

Id. at 1357. The court then noted that the Board had failed to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested" the invention. *Id.* (emphasis added). In *In Re Werner Kotzab*, 217 F.3d 1365; 2000 U.S. App. LEXIS 15504; 55 USPQ2d 1313 (Fed. Cir. 2000), the Federal Circuit reiterated that:

> [A] rejection cannot be predicated on the mere identification in . . . [the cited reference] of individual components of claimed limitations. Rather, ***particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.***

In re Kotzab, at 1369-1372 (emphasis added).

The closest that the Office Action comes to pointing out specific motivation for the Brown-Smith combination is the citation of Smith's teaching regarding the use of ligation-mediated PCR products to probe a polynucleotide array. The Examiner concludes that "[t]his expressly

demonstrates that the PCR products of Smith can be used in conjunction with high-density grids (*e.g.*, polynucleotide arrays)." Office Action, page 8. However the claims require more than "use in conjunction with" polynucleotide arrays. The claims require the application of "target solutions comprising the amplification products to one or more substrates, . . . whereby target solution polynucleotides are immobilized on the substrate(s) to form the target elements of an array of polynucleotides." Smith does not provide specific motivation for this use of ligation-mediated PCR amplification products.

B. Claim 1 requires the use of the recited amplification products as target polynucleotides, which are distinct from probe polynucleotides.

It appears that the underlying basis for the previous disagreement on this point is the claim language used to describe the use of the amplification products to form an array of polynucleotides. In the Office Action, the Examiner stated:

> [I]f Smith teaches that his PCR products "probe conventionally created DNA arrays", then his PCR products would necessarily be considered an "array of polynucleotides". . . because conventionally created DNA arrays are based on polynucleotides arrayed at distinct locations on a substrate, and therefore, the probing of these arrays would result in an array of polynucleotides . . . . In other words, Applicants appear to assert that the PCR products must be arrayed spotted [*sic*] on the substrate (e.g., not through a probe); however the claims do not require this, as the claims only require that the target solutions be "applied" to a substrate to produce an "array" of polynucleotides.

Office Action, page 9.

Applicants believe that one skilled in the art would not have interpreted the claims as the Examiner has done. In particular, the following excerpts from Applicants' specification make it clear that the target solutions are applied to a substrate to form the target elements of an array that can then be probed by hybridization with labeled polynucleotides.

At page 6, lines 22-27, the specification states:

> ***The elements of an array are termed "target elements."***
>
> As used herein with reference to target elements, the term "distinct location" means that each element is physically separated from every other target element such that ***a signal (e.g., a fluorescent signal) from a labeled molecule bound to target element*** can be uniquely attributed to binding at that target element.

(Emphasis added.) This passage makes it clear that an array according to the invention has target elements that retain hybridization capacity. Hybridizing probe polynucleotides to an array of polynucleotides reduces, and potentially eliminates, hybridization capacity of the target elements. Therefore, "applying target solutions comprising the amplification products. . . to produce an array of polynucleotides," as previously recited in the claims, does not read on Smith's disclosure of using amplification products to probe an array.

> At page 17, lines 17-23, the specification states:
>
> An array according to the invention can include target elements of any dimensions suitable for the intended application. ***Small target elements containing small amounts of concentrated target polynucleotides are conveniently used when the probe that is hybridized to them*** contains high complexity polynucleotides, since the total amount of probe available for binding to each target element during hybridization to the array will be limited.

(Emphasis added.) This passage reinforces the concept that the target elements of an array according to the invention contain target polynucleotides to which probe polynucleotides are hybridized when the array is used.

Page 15, lines 12-14 of the specification states: "The target solutions of the invention can each be applied to a distinct location on a substrate to produce an array of polynucleotide-containing target elements." Interpreting this passage in a manner that is consistent with the passages quoted above, the target solutions are applied to a substrate so as to create the target elements of an array, *i.e.*, the amplification products of the target solutions become the target polynucleotides that can then be hybridized with probe polynucleotides.

> At page 14, lines 14-19, the specification states:
>
> To form target solutions, the polynucleotide products of ligation-mediated amplification are isolated by any convenient method, such as, for example, precipitation by ethanol. Each polynucleotide product is resuspended to form a target solution suitable for application to a substrate. ***Suitable solutions should not significantly diminish the hybridization capacity of the polynucleotide products and should enable the polynucleotide products to adhere to the substrate.***

(Emphasis added.) This passage makes it clear that the polynucleotides of the target solutions must have (1) the ability to adhere to a substrate, and (2) the ability to hybridize to complementary or substantially complementary polynucleotides. These two requirements are consistent with the use of

these polynucleotides as target polynucleotides and inconsistent with their use as probe polynucleotides. More specifically, probe polynucleotides should not adhere to the substrate, as such adherence would produce a non-specific signal that would obscure the signal attributable to hybridization to target polynucleotides. Thus, the term "target solutions" does not read on a solution of polynucleotides that is used to probe an array, as taught by Smith.

Although it is believed that the previously pending claims clearly distinguished the Brown-Smith combination, Applicants have amended claim 1 to even more clearly exclude the use of the target solutions to probe an array. Specifically, claim 1(d) now recites: "applying target solutions comprising the amplification products to one or more substrates, . . . whereby target solution polynucleotides are immobilized on the substrate(s) to form the target elements of an array of polynucleotides." As noted above, a "target solution" is not a probe solution. Neither Brown, nor Smith teaches or suggests the use of ligation-mediated PCR products in a target solution.

With respect to immobilization on a substrate, Applicants' specification teaches:

> Many methods for immobilizing polynucleotides on a variety of substrates are known in the art. The polynucleotide products described herein can be covalently or noncovalently bound to the substrate. The substrate surface can be prepared for immobilization using any of a variety of different materials, for example as laminates, depending on the desired properties of the array. Proteins (e.g., bovine serum albumin) or mixtures of macromolecules (e.g., Denhardt's solution) can be employed to avoid non-specific binding, simplify covalent conjugation, enhance signal detection or the like. If covalent bonding between a polynucleotide and the substrate surface is desired, the surface can be polyfunctional or capable of being polyfunctionalized. Functional groups useful for covalently bonding polynucleotides to substrate surfaces include carboxylic acids, aldehydes, amino groups, cyano groups, ethylenic groups, hydroxyl groups, mercapto groups, and the like. Alternatively, such functional groups can be introduced into the polynucleotide products of the invention. Methods for introducing various functional groups into polynucleotides are well-known and described, for example, in Bischoff et al., Anal. Biochem. (1987) 164:336-344; Kremsky et al., Nuc. Acids Res. (1987) 15:2891-2910. Nucleotides bearing functional groups can also added to the products of the ligation-mediated amplification method described above using PCR primers containing a modified nucleotide, or by enzymatic end-labeling with modified nucleotides. In a preferred embodiment, polynucleotide products according to the invention bear a functional group, such as, for example, an amino group.

The target solutions of the invention are applied to the substrate surface using any method that substantially maintains the hybridization capacity of the target solution polynucleotides.

Applicants' specification, page 16, lines 5-27 (emphasis added). This passage further emphasizes that the amplification products of the target solutions are immobilized on the surface of the substrate so as to preserve their hybridization capacity, consistent with their use as target polynucleotides and not as probe polynucleotides. Neither Brown, nor Smith teaches or suggests this type of immobilization of ligation-mediated PCR products on a substrate.

Finally, as recited in amended claim 1, target solution polynucleotides are immobilized on a substrate "to form the target elements of an array of polynucleotides." The foregoing establishes that "the target elements of an array of polynucleotides" refers to polynucleotides that are arrayed on a substrate and have the capacity to hybridize to probe polynucleotides. Accordingly, claim 1 relates to forming arrays containing target elements produced using the recited amplification method (*e.g.*, ligation-mediated PCR). By contrast, Smith and Brown, taken together, describe conventional arrays that can be probed with the products of ligation-mediated PCR. After hybridization, the conventional array has ligation-mediated PCR products hybridized to the target elements. In this case, the ligation-mediated PCR products cannot serve as "target elements" because they have no capacity to hybridize to anything else. This additional aspect of claim 1 further distinguishes the Brown-Smith combination

In summary, as the Examiner recognizes, Brown discusses polynucleotide array fabrication, but does not contemplate the use of ligation-mediated PCR to form the target elements of an array. Smith describes ligation-mediated PCR, and contemplates the use of ligation-mediated PCR products to probe polynucleotide arrays. Smith notes advantages of ligation-mediated PCR, but neither Smith, nor Brown provide any specific motivation to use ligation-mediated PCR to form target elements of a polynucleotide array, as recited in claim 1. Accordingly, the Brown-Smith combination clearly fails to satisfy the second element of a *prima facie* case of obviousness with respect to claim 1.

III. NEITHER THE REFERENCE(S), NOR THE KNOWLEDGE IN THE ART PROVIDES A REASONABLE EXPECTATION THAT THE INVENTION OF CLAIM 1 WOULD WORK.

Turning to the third element of a *prima facie* case, the Examiner states

> Applicants' argument that the Brown-Smith combination does not provide a reasonable expectation of success is also not persuasive. Applicants' arguments and Dr. Albertson's declaration have been considered, and it appears as if Applicants are arguing that the actual spotting of the PCR products occurs directly on an array, and that it is this "direct spotting" (e.g., not through a probe) that was unexpected at the time of the invention.
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> * * *
>
> However, the claims are not directed to spotting the target solutions directly onto the array (and not through a probe, for example). Accordingly, the experiment detailed by the Albertson declaration is not commensurate in scope with the claims, and therefore is not persuasive. See MPEP 716.

Office Action, page 10. To clarify, the Declaration of Dr. Albertson, dated October 14, 2003 establishes the unpredictability of success in using particular amplification methods to produce target solutions that could be immobilized on one or more substrate(s) to form the target elements of an array of polynucleotides. For the reasons discussed above, claim 1 does not read on "applying" PCR products to an array "through a probe," as the Examiner suggests. Rather, claim 1 relates to performing the recited specific amplification method to produce target solutions, followed by "applying target solutions comprising the amplification products to one or more substrates, . . . whereby target solution polynucleotides are immobilized on the substrate(s) to form the target elements of an array of polynucleotides." As Dr. Albertson's Declaration is commensurate with the scope of the claims, this Declaration must be given due consideration.

In the Declaration, Dr. Albertson explains that, in developing the invention, the inventors tried two different amplification-based methods for producing target solutions for arrays, as well as one method that did not employ amplification. Dr. Albertson states:

> We decided to test the following three techniques for producing P1 or BAC DNA target solutions: (1) fragmenting the P1 or BAC DNA using sonication or chemical treatments of the DNA; (2) ligation-mediated polymerase chain reaction (PCR); and (3) "shotgun cloning" the P1 or BAC inserts into a DNA sequencing vector, followed by PCR amplification of the ligation mixture. ***In advance of these studies, we could not predict whether any of these techniques would yield sufficiently representative target solutions. In particular, we could not be sure that the amplification-based techniques would satisfy this requirement***, as essentially all of the starting P1 BAC DNA sequences would have to be amplified to essentially the same

> extent to produce an amplification product (and, ultimately, target solution) in which the P1 or BAC DNA sequences were present in approximately the same proportions as in the starting P1 or BAC DNA.
>
> ***Prior to carrying out these studies, my expectation was that the third approach, shotgun cloning, followed by PCR, was the most likely to give satisfactory results. In fact, . . . this approach failed absolutely. However, the second approach, based on ligation-mediated PCR, worked unexpectedly well.***

Albertson Declaration dated October 14, 2003, page 2 (emphasis added). In particular, shotgun cloning, followed by PCR, yielded target solutions that, when spotted on a substrate and hybridized with probe, gave "very low" hybridization intensities, rendering this method unsuitable for preparing target solutions for arrays. *Id.* at page 13. According to Dr. Albertson, "[t]his result demonstrates the difficulty in this field of predicting what technique will work for a particular application, based only on a theoretical understanding of the technique and/or information about its suitability for different applications." *Id.* at page 14. By contrast, "the ligation mediated PCR approach worked unexpectedly well, producing target solutions that, when spotted and hybridized with a labeled probe, produced a signal that is essentially the same as the signal obtained from the starting polynucleotide." *Id.* Dr. Albertson concludes: "As the failure of the shotgun cloning approach demonstrates, this result could not have been predicted based on the available information concerning ligation-mediated PCR." Thus, Dr. Albertson's Declaration shows the results of testing two specific amplification methods to determine their suitability for use in preparing target solutions for polypeptide array fabrication. The one exemplifying the claimed method worked, whereas the other one did not. Accordingly, this Declaration unequivocally establishes (1) the unpredictability of success in using particular amplification methods to produce target solutions; and (2) that the method corresponding to that recited in claim 1 worked unexpectedly well.

In summary, Applicants maintain that the Examiner has not established a *prima facie* case of obviousness of claim 1 because the record fails to provide any of the elements of a *prima facie* case. In particular, as explained above, Smith provides no motivation for forming arrays, as described in Brown, containing target elements produced using ligation-mediated PCR. Dr. Albertson's Declaration demonstrates the unpredictability in this field, which negates any reasonable expectation of success. Accordingly, the foregoing makes it clear that the second and third elements of a *prima facie* case are lacking.

IV. THE RECORD ESTABLISHES THAT THE INVENTION OF CLAIM 1 WORKED UNEXPECTEDLY WELL.

Moreover, even assuming *arguendo* that a *prima facie* case had been established, Applicants submit that Dr. Albertson's Declaration provides evidence of unexpected results, which is a "secondary consideration" sufficient to rebut any *prima facie* case of obviousness. As stated by the Court of Appeals for the Federal Circuit in *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-663 (Fed. Cir. 2000):

> In order to determine obviousness as a legal matter, four factual inquiries must be made concerning: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) secondary considerations of nonobviousness, which in case law is often said to include commercial success, long-felt but unresolved need, failure of others, copying, and ***unexpected results***. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. (BNA) 459, 467, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 877, 27 U.S.P.Q.2D (BNA) 1123, 1128 (Fed. Cir. 1993).

Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness. . . . Indeed, in Stratoflex, we said:

> ***Evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.*** It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art.

Stratoflex, 713 F.2d at 1538, 218 U.S.P.Q. (BNA) at 879.

Ruiz v. A.B. Chance Co., 234 F.3d 654, 662-663 (Fed. Cir. 2000) (emphasis added). Dr. Albertson's testimony that "the second approach, based on ligation-mediated PCR, worked unexpectedly well" establishes that the results embodied the method of claim 1 were unexpected. Accordingly, even if the Examiner maintains that the cited references are sufficient to establish a *prima facie* case of obviousness, Dr. Albertson's Declaration provides undeniable evidence of the secondary consideration of unexpected results. In the face of this evidence, the § 103 rejection of claim 1 cannot properly be maintained.

V. THE EXAMINER'S RELIANCE ON PINKEL (NATURE GENETICS) IS MISPLACED.

In addition to rejecting Dr. Albertson's Declaration as not commensurate with the scope of the claims, the Examiner indicated that the Declaration was not persuasive in light of Pinkel et al. (Nature Genetics (1998) 20:207-11). Specifically, the Examiner stated:

> Assuming that Applicants are purporting that there is not a reasonable expectation of success of spotting high molecular [weight] DNAs, such as BAC[s], directly onto the arrays (and not through probes, for example), Applicants' arguments are also not persuasive. For example, in 1998, the inventors of the instant application demonstrated that BAC DNA could be bound effectively and directly to an array (see Pinkel et al. (Nature Genetics (1998) 20:207-11), especially column 2 of page 210.

Office Action, page 11. The passage cited by the Examiner describes array fabrication using P1 or BAC clones. The passage states: "Cloned genomic DNA for targets was isolated from bacterial cultures (500 ml) using Qiagen maxi kits (12162) following the instructions of the manufacturer, except that the volume of lysis buffer was increase 1.5-2-fold." A printout from Qiagen's internet site is attached as Exhibit A. This printout indicates that the "Qiagen Plasmid Maxi Kit" relies on anion-exchange to purify DNA. The flowchart shown on page 2 of Exhibit A indicates that no amplification is performed in using the Maxi Kit. Pinkel (Nature Genetics) goes to state that the purified DNA was ethanol precipitated and then dissolved in water and DMSO plus nitrocellulose to form target solutions. Pinkel (Nature Genetics), page 210, col. 2. According to the article, "[q]uadruplicate spots (200-400 μm in diameter) of each target solution were made by depositing the target solutions onto slides using capillary tubes." *Id.* Thus, the target polypeptides for the disclosed arrays were not amplified.

By contrast, claim 1 relates to the use of the recited specific amplification method to prepare target polypeptides. As noted above, Dr. Albertson's Declaration establishes (1) the unpredictability of success in using particular amplification methods to produce target polypeptides; and (2) that the method corresponding to that recited in claim 1 worked unexpectedly well. That non-amplified BAC or P1 DNA could be used to form target elements of a polypeptide array, as described in Pinkel (Nature Genetics), does not suggest that it would even be feasible to amplify such DNA as recited in claim 1 to form target elements. Accordingly, Pinkel (Nature Genetics) does not rebut the Albertson Declaration.

VI. CONCLUSION

Claim 1 is patentable over the combination of Brown and Smith because the Examiner has failed to establish a *prima facie* case of obviousness over this combination of references or, in the alternative, because any *prima facie* case has been rebutted by the Declaration of Dr. Albertson establishing that the claimed method worked unexpectedly well. The other rejected claims that remain pending all depend, directly or indirectly from claim 1, and are therefore patentable over the cited combination for at least these reasons. Accordingly, the withdrawal of the § 103 rejection of claims 1, 3-16, 23 and 25 is respectfully requested.

BROWN, SMITH, AND GORDON

Claim 17 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al., in view of Smith, and further in view of Gordon et al. (USPN 5,601,980). Office Action, page 11. This rejection is respectfully traversed.

Claim 17 depends ultimately from claim 1 and recites a method "wherein the target solutions are robotically spotted on the substrate." Gordon was cited for the teaching of robotic spotting. *Id.* However, Gordon fails to remedy the deficiencies of the Brown-Smith combination with respect to claim 1. Specifically, none of the cited references provides any motivation for forming arrays, as described in Brown, containing target elements produced using the ligation-mediated PCR method of Smith. Similarly, none of the references provides any reasonable expectation that such an approach to array fabrication would be successful. In addition, the Declaration of Dr. Albertson dated October 14, 2003 establishes the unexpected success of the method recited in claim 1 and incorporated into claim 17 by virtue of its dependence from claim 1. Applicants therefore respectfully request withdrawal of the § 103 rejection of claim 17.

BROWN, SMITH, AND STIMPSON

Claim 18 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al., in view of Smith, and further in view of Stimpson (Proc. Natl. Acad. Sci. USA (1995) 92:6370-83). Office Action, page 13. This rejection is respectfully traversed.

Claim 18 depends ultimately from claim 1, which recites the use of adaptors in the claimed amplification reaction. Claim 18 recites that "at least one strand of the adapters includes an

amino group." Stimpson was cited as teaching "DNA chips (i.e., array[s]), which are constructed by using 3'-amino-labeled oligonucleotides." Office Action, page 13. However, Stimpson discloses that "DNA chips . . . were constructed by using ***presynthesized*** 3'-amine-labeled oligonucleotides." Stimpson, page 6380, col. 1 (emphasis added). Stimpson thus fails to teach or suggest anything regarding any amplification-based method for producing target solutions for an array, much less the specific amplification steps recited in claim 1. Stimpson thus fails to remedy the deficiencies of the Brown-Smith combination with respect to claim 1. Specifically, none of the cited references provides any motivation for forming arrays, as described in Brown, containing target elements produced using the ligation-mediated PCR method of Smith. Similarly, none of the references provides any reasonable expectation that such an approach to array fabrication would be successful. In addition, the Declaration of Dr. Albertson dated October 14, 2003 establishes the unexpected success of the method recited in claim 1 and incorporated into claim 18 by virtue of its dependence from claim 1. Applicants therefore respectfully request withdrawal of the § 103 rejection of claim 18.

BROWN, SMITH, AND CRONIN OR PINKEL (USPN 5,837,196)

Claims 19, 21, and 24 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Brown et al., in view of Smith, and further in view of Cronin et al (WO 97/43450) or Pinkel et al (USPN 5,837,196). Office Action, page 14. This rejection is moot as to claims 21 and 24, which have been cancelled. As to claim 19, the rejection is respectfully traversed.

Claim 19 depends from claim 1 and recites a method "wherein the target solutions comprise dimethyl sulfoxide [DMSO] at a concentration of about 20% by volume." Cronin and Pinkel were cited as teaching target solutions containing DMSO. Office Action, page 9. Cronin fails to teach or suggest the amplification steps of claim 1 and is devoid of any teaching regarding the arraying of target solutions containing amplification products produced in this manner. Cronin, like Stimpson, discloses arrays of synthetically produced oligonucleotides. Cronin, page 9, line 15 – page 10, line 29.

With respect to amplification, Pinkel teaches:

> If the tissue sample is small, so that a small amount of nucleic acids is available, amplification techniques such as the polymerase chain reaction (PCR) using degenerate primers can be used. For a general description of PCR, see, PCR Protocols, Innis et al. eds. Academic

> Press, 1990. In addition, PCR can be used to selectively amplify sequences between high copy repetitive sequences. These methods use primers complementary to highly repetitive interspersed sequences (e.g., Alu) to selectively amplify sequences that are between two members of the Alu family (see, Nelson et al., Proc. Natl. Acad. Sci. USA 86:6686 (1989)).

Thus, Pinkel also fails to teach or suggest the amplification steps recited in claim 1 and, consequently, neither teaches nor suggests arraying the resultant amplification products.

Therefore, none of the cited references provides any motivation for forming arrays, as described in Brown, containing target elements produced using the ligation-mediated PCR method of Smith. Similarly, none of the references provides any reasonable expectation that such an approach to array fabrication would be successful. In addition, the Declaration of Dr. Albertson dated October 14, 2003 establishes the unexpected success of the method recited in claim 1 and incorporated into claim 19 by virtue of its dependence from claim 1. Applicants therefore respectfully request withdrawal of the § 103 rejection of claim 19.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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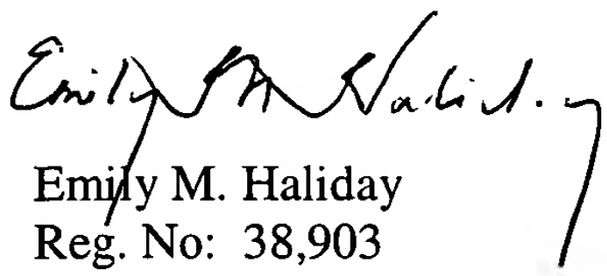
Respectfully submitted,



Emily M. Haliday
Reg. No: 38,903

EXHIBIT A

QIAGEN Plasmid Maxi Kit

For purification of up to 500 ug ultrapure plasmid or cosmid DNA

- Purity equivalent to that obtained by 2 x CsCl-gradient centrifugation
- Reproducible yields of ultrapure plasmid DNA
- No ethidium bromide, phenol, chloroform, or CsCl
- Cost-effective preparations

▲ Hide detailed information

Classic QIAGEN Plasmid Maxi Kits use gravity-flow QIAGEN-tip 500 anion-exchange tips for efficient purification of plasmid DNA. QIAGEN-tips 500 are also available separately.

QIAGEN Plasmid Maxi Kit Specifications

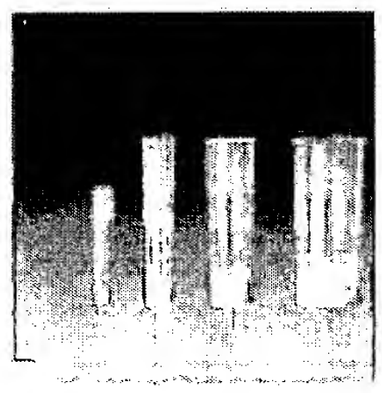
Expected yield*	Column capacity	Culture vol
Up to 500 µg	500 µg	100 ml –5C

** Actual yields depend on plasmid copy number, size of insert, host strain, culture me culture volume.*

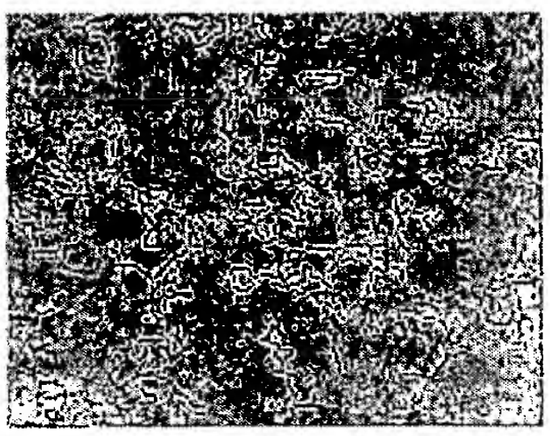
† Culture volumes depend on plasmid copy number, size of insert, host strain, and cul

Principle

The unique anion-exchange resin in QIAGEN-tips is developed exclusively for the purification of nucleic acids. Its exceptional separation properties result in DNA purity equivalent or superior to that obtained by two successive rounds of CsCl gradient centrifugation (see Figure "Ultrapure Plasmid DNA Yielded by QIAGEN Plasmid kits"). Pre-packed QIAGEN-tips operate by gravity flow and never run dry, minimizing the hands-on time required for plasmid preparation. The entire QIAGEN plasmid purification system avoids the use of toxic substances such as phenol, chloroform, ethidium bromide, and CsCl, minimizing hazar user and the environment.



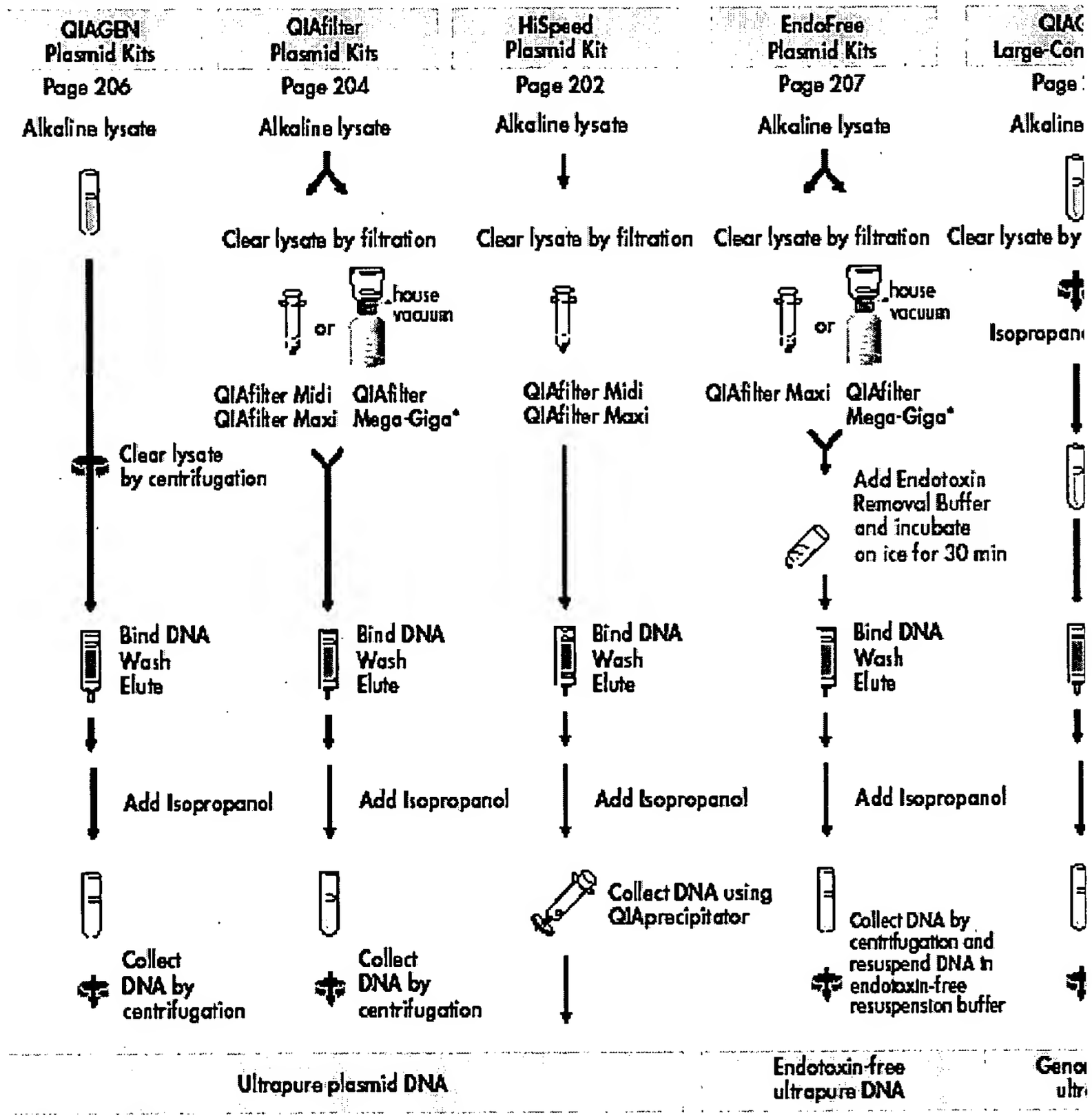
Ultrapure Plasmid DNA Yielded by QIAGEN Plasmid kits



Electron micrograph of pCMVLuc DNA prepa QIAGEN-tip 2500. (Data kindly provided by German Cancer Research Center, Heidelber

Procedure

With QIAGEN Plasmid Kits, bacterial lysates are cleared by centrifugation. The cleared then loaded onto the anion-exchange tip where plasmid DNA selectively binds under a low-salt and pH conditions. RNA, proteins, metabolites, and other low-molecular-weigh are removed by a medium-salt wash, and ultrapure plasmid DNA is eluted in high-salt flowchart). The DNA is concentrated and desalted by isopropanol precipitation and coll centrifugation.

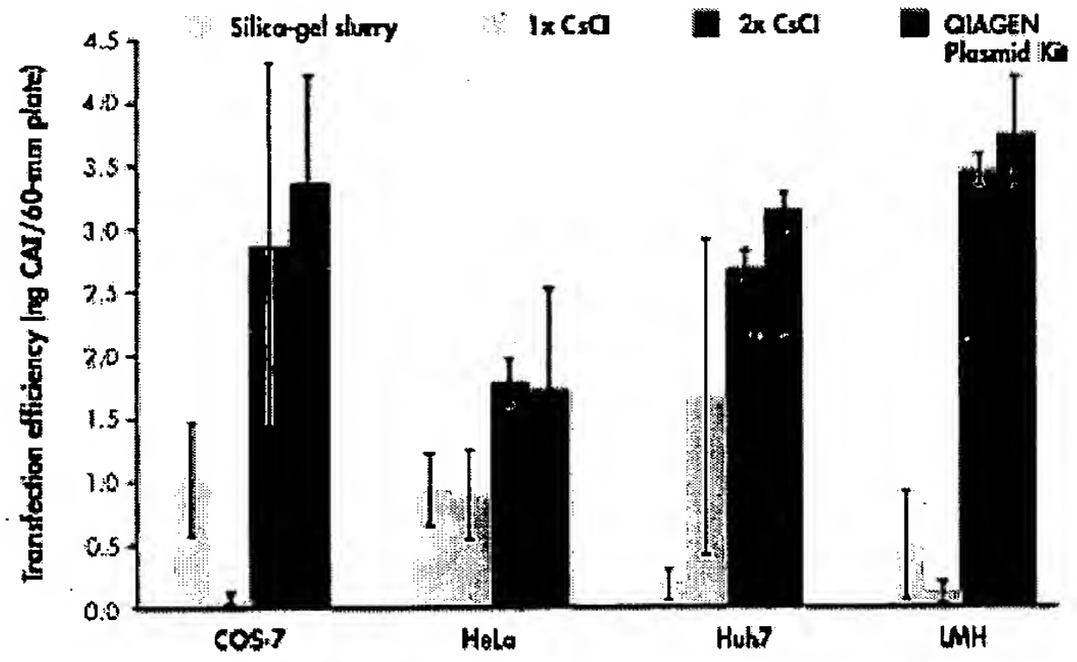


Applications

Plasmid DNA purified with QIAGEN Plasmid Kits is ideal for use in applications such as (see figure "Transfection Efficiency vs Plasmid Purification Method "), cloning, manual sequencing, including capillary sequencing, and in vitro transcription.

Transfection Efficiency vs Plasmid Purification Method

Different pRSVcat D preparations using indicated were intrc the indicated cell lir liposome-mediated and the efficiencies by measuring CAT e after 40 h. Each ba



the mean of 4 indep transfections (2 tra with each of 2 indep plasmid preparatior

Ordering Information

Add to Cart?	Name	Details	Cat. N
☐	QIAGEN Plasmid Maxi Kit (10)	10 QIAGEN-tip 500, Reagents, Buffers	12162
☐	QIAGEN Plasmid Maxi Kit (25)	25 QIAGEN-tip 500, Reagents, Buffers	12163
☐	QIAGEN Plasmid Maxi Kit (100)	100 QIAGEN-tip 500, Reagents, Buffers	12165

Add to Cart